## REMARKS

I. Introduction

The referenced application is a continuation prosecution application ("CPA"), filed January 9, 2001, under 37 C.F.R. §1.53(d) based on parent Application Serial No. 08/945,425.

Applicants are appreciative of the Interview with Examiners Desai and Rotman which occurred on April 10, 2001 and as summarized in the Interview Summary of record.

II. Claim Amendments

The claims have been amended by deleting the non-elected species of Groups II-IV as summarized in the Office Action, mailed April 30, 1999 (Paper No. 5). Applicants reserve the right to file divisional applications directed to the deleted non-elected species. Applicants submit that it is not necessary to amend the inventorship pursuant to 37 C.F.R. §1.48(b) in view of the deletion of the non-elected species. Each of the currently named inventors is an inventor of at least one of the pending claims.

Accordingly, the amended claims are limited to the elected species of Group I, wherein $Het_1$ is a substituted pyridine and $Het_2$ is a benzimidazole. Moreover, the claims have been amended where appropriate by deleting the expression "an administration regimen" and substituting therefor -- a method -- of or for treatment.

New claims 26 and 27 are directed to embodiments of canceled claims 16 and 25, respectively.

No new matter has been introduced by the claim amendments.

III. The Claimed Invention

The claimed invention is directed to an improved method of treatment (claims 1-6, 18, 26 and 27) and oral pharmaceutical formulation (claims 7-11 and 19). Specifically, the claimed method relates to a method for improving the treatment of gastrointestinal disorders associated with gastric acid secretion comprising the oral administration of a pharmaceutical formulation comprising a therapeutically effect amount of an acid labile $H^+$, $K^+$-ATPase inhibitor of the Formula I, wherein the improved method induces an extended blood plasma profile of the $H^+$, $K^+$-ATPase inhibitor. The claimed oral pharmaceutical formulation comprises an acid labile $H^+$, $K^+$-ATPase inhibitor of the Formula I and a pharmaceutically acceptable carrier, wherein the formulation induces an extended blood plasma profile of the $H^+$, $K^+$-ATPase inhibitor.

The expression "blood plasma profile" as used throughout the specification and in the claims, and as understood by the person of ordinary skill in the art, means the measurable concentration of the $H^+$, $K^+$-ATPase inhibitor at any time subsequent to administration.

It is Applicants' invention that the unprecedented administration and formulation inducing an extended blood plasma profile of the $H^+$, $K^+$-ATPase inhibitor has an unexpected improvement in the inhibition of gastric acid secretion, as shown in Example 1.

IV. Claim Rejection - 35 U.S.C. §102

The novelty rejections of record are as follows: claims 1-11, 15, 16, 18-21 and 23-25 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Nos. 5,753,265 to Bergstrand et al. (the "265 patent") and U.S. Patent No. 5,817,338 to Bergstrand et al. (the "'338 patent").

In connection with the §102 rejections, Applicants rely on their comments of record distinguishing the claimed invention over each of the '265 and '338 patents (See Letter, mailed June 9, 2000; Amendment, mailed October 28, 1999). For the same reasons, and as noted in the Interview Summary, the §102 rejections will be dropped since the coatings of the multiple units of the tablets of the cited '265 and '338 patents would not provide an extended blood plasma profile of the H+, K+-ATPase inhibitor as claimed.

Accordingly, Applicants respectfully request and are appreciative of the withdrawal of the rejections under 35 U.S.C. §102(e).

V. Claim Rejection - 35 U.S.C. §103

The obviousness rejections of record have been maintained. Accordingly, claims 1-11, 15, 16, 18-21 and 23-25 are rejected under 35 U.S.C. §103(a) as being unpatentable over the following:

1. the '265 and '338 patents;
2. Patent No. 5,330,982 to Tyers; and
3. the '265 patent in combination with the following secondary references: (a) the '124 patent to Sachs et al.; (b) Remington's Pharmaceutical Sciences, John Hoover, 1975, p. 702; (c) Scand. J. Gastroenterol., Lind et al. 1986, p.137-138; (d) Scand. J. Gastroenterol., Lind et al., 1988, 23, p.1259-1266; and (e) Lind et al., Gut, 1983, p. 270-276.

In connection with the §103 rejections, Applicants rely on their comments of record distinguishing the claimed invention over each of the cited references (See Letter, mailed June 9, 2000; Amendment, mailed October 28, 1999).

Comparative data evidencing the unexpected and superior result that is possible with the claimed invention is provided by the Example and Figure of the subject application. As described in the Example at pages 10-11, the pharmacological effect of the claimed method of treatment was compared with a conventional administration regimen involving omeprazole racemate (Prilosec® capsules). Pursuant to the invention, a first group of subjects received 20 mg of omeprazole twice daily with 3 hours apart from each administration. A second group of subjects received a 40 mg daily dose of omeprazole. With each group of subjects, the efficacy of the respective method of treatment in controlling acid secretion was measured. As shown in the Figure, the therapeutic effect of omeprazole is maximized, particularly on "day 1", when the blood plasma concentration of the drug is extended by repeated single doses of omeprazole which are administered with 3 hours apart from each administration.

Applicants submit that the substantial improvement in efficacy as shown in Figure 1 is evidence of a patentable discovery. In view of the known prolonged degree and duration of acid inhibition, e.g., 3-4 days, it was indeed unexpected that a method comprising a repeated administration or a dosage form which provides an extended blood plasma concentration of an $H^+$, $K^+$-ATPase inhibitor, as claimed, would have an improved pharmacological effect in the inhibition of gastric acid secretion.

As noted in the Interview Summary, Applicants were requested to provide a side-by-side comparison with the tablet dosage form of the cited '265 patent. However, as discussed at the Interview, the multiple unit tablet composition of omeprazole of the '265 patent and the capsule dosage form of omeprazole (Prilosec® capsules) of the Example are bioequivalent. A discussion supporting the bioequivalency of the Prilosec® capsules and the tablet dosage form '265 patent is set forth in the accompanying Declaration of Dr. Cederberg. Therefore, the conclusion supported

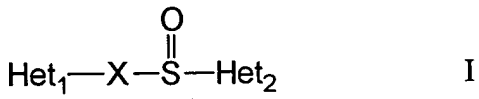
by the Example and Figure regarding the unexpected advantages of the claimed invention apply equally to the multiple unit tablet composition of omeprazole of the '265 patent.

Additionally, with specific regard to the §103 rejection based on Tyers, Applicants also rely on the remarks appearing on page 27 of the Amendment, mailed October 28, 1999. Apparently, those remarks were convincing since the rejection based on Tyers was dropped and not repeated in the final Office Action, mailed December 10, 1999 (Paper No. 10).

Accordingly, for all of the foregoing reasons, Applicants respectfully request the withdrawal of the §103 rejections.

VI. Mark-up of amended claims showing insertions and deletions:

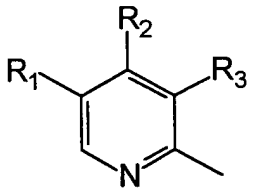
1. (Thrice amended) A method of treatment for improving the inhibition of gastric acid secretion [An administration regimen for improved inhibition of gastric acid secretion] comprising the oral administration of a pharmaceutical formulation comprising a therapeutically effective amount of an acid labile $H^+$, $K^+$-ATPase inhibitor, wherein the method [administration regimen] induces an extended blood plasma profile of the $H^+$, $K^+$-ATPase inhibitor, and the $H^+$, $K^+$-ATPase inhibitor is a compound of the formula I



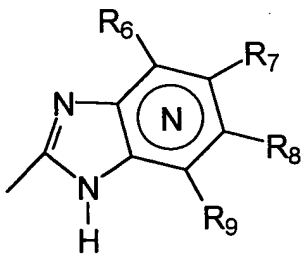
I

wherein

$Het_1$ is



$Het_2$ is



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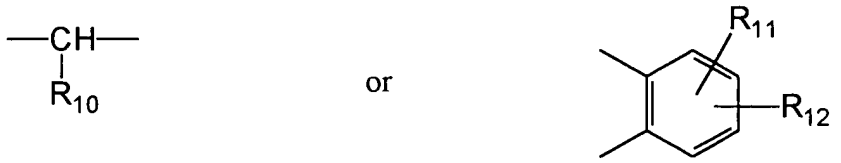


or

wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by $R_6$-$R_9$ optionally may be exchanged for a nitrogen atom without any substituents;

$R_1$, $R_2$ and $R_3$ are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

$R_6$-$R_9$ are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups $R_6$-$R_9$ form ring structures which may be further substituted;

$R_{10}$ is hydrogen or forms an alkylene chain together with $R_3$; and

$R_{11}$ and $R_{12}$ are the same or different and selected from the group consisting of hydrogen, halogen or alkyl.

2. (Twice amended) The method [admimistration regimen] according to claim 1 or 26, wherein the $H^+$, $K^+$-ATPase inhibitor is a compound selected from the group consisting of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole.

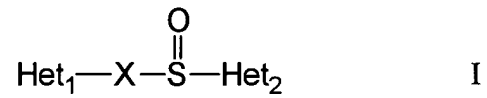
3. (Twice amended) The method [administration regimen] according to claim 1 or 26, wherein the extended blood plasma profile is obtained by two or more consecutive oral administrations of a unit dose of the $H^+$, $K^+$-ATPase inhibitor with 0.5 - 4 hours intervals.

4. (Twice amended) The method [administration regimen] according to claim 1 or 26, wherein the extended blood plasma profile is obtained by oral administration of the pharmaceutical formulation which releases the $H^+$, $K^+$-ATPase inhibitor for absorption in two or more discrete pulses separated in time by 0.5 - 4 hours.

5. (Thrice amended) The method [administration regimen] according to claim 1 or 26, wherein the extended blood plasma profile is obtained by oral administration of the pharmaceutical formulation which releases the $H^+$, $K^+$-ATPase inhibitor for absorption with an almost constant rate during an extended time period [and the extended plasma profile is maintained for 2-12 hours].

6. (Thrice amended) The method [administration regimen] according to any of claims 1-5 or 26 [1 - 4], wherein the extended blood plasma profile is maintained for 2 - 12 hours.

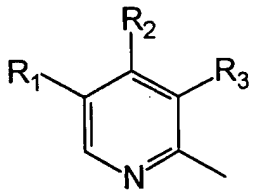
7. (Thrice amended) An oral pharmaceutical formulation comprising an acid labile $H^+$, $K^+$-ATPase inhibitor and a pharmaceutically acceptable carrier, wherein the formulation induces an extended blood plasma profile of the $H^+$, $K^+$-ATPase inhibitor, and the $H^+$, $K^+$-ATPase inhibitor is a compound of the formula I



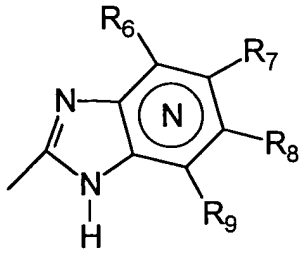
I

wherein

$Het_1$ is



$Het_2$ is



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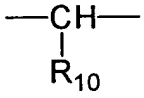

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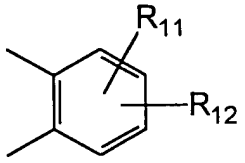


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by $R_6$-$R_9$ optionally may be exchanged for a nitrogen atom without any substituents;

$R_1$, $R_2$ and $R_3$ are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

$R_6$-$R_9$ are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups $R_6$-$R_9$ form ring structures which may be further substituted;

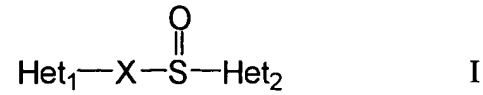
$R_{10}$ is hydrogen or forms an alkylene chain together with $R_3$; and

$R_{11}$ and $R_{12}$ are the same or different and selected from the group consisting of hydrogen, halogen or alkyl.

10. (Thrice amended) The oral pharmaceutical formulation according to claim 7, wherein the pharmaceutical formulation releases the $H^+$, $K^+$-ATPase inhibitor for absorption with an almost constant rate during an extended time period [and the extended plasma profile is maintained for 2-12 hours].

11. (Thrice amended) The oral pharmaceutical formulation according to any of claims 7-10 [7 - 9], wherein the extended blood plasma profile is maintained for 2 -12 hours.

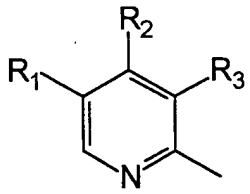
18. (Twice amended) A method of treatment for improving the inhibition of gastric acid secretion [An administration regimen for improved inhibition of gastric acid secretion] comprising the oral administration of a pharmaceutical formulation comprising a therapeutically effective amount of an acid labile $H^+$, $K^+$-ATPase inhibitor, wherein the method [administration regimen] induces an extended blood plasma profile of the $H^+$, $K^+$-ATPase inhibitor, and the $H^+$, $K^+$-ATPase inhibitor is a compound of the formula I



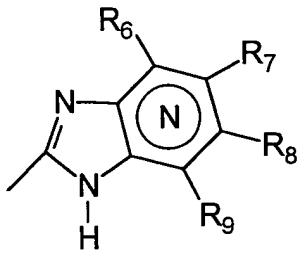
I

wherein

$Het_1$ is



$Het_2$ is



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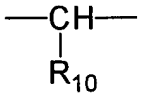

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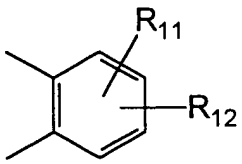


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by $R_6$-$R_9$ optionally may be exchanged for a nitrogen atom without any substituents;

$R_1$, $R_2$ and $R_3$ are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

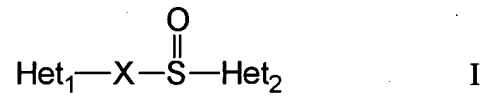
$R_6$-$R_9$ are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups $R_6$-$R_9$ form ring structures which may be further substituted;

$R_{10}$ is hydrogen or forms an alkylene chain together with $R_3$; and

$R_{11}$ and $R_{12}$ are the same or different and selected from the group consisting of hydrogen, halogen or alkyl

with the proviso that the $H^+$, $K^+$-ATPase inhibitor is not pantoprazole.

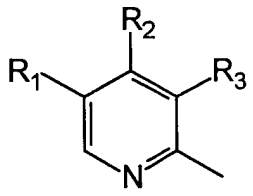
19. (Twice amended) An oral pharmaceutical formulation comprising an acid labile $H^+$, $K^+$-ATPase inhibitor and a pharmaceutically acceptable carrier, wherein the formulation induces an extended blood plasma profile of the $H^+$, $K^+$-ATPase inhibitor, and the $H^+$, $K^+$-ATPase inhibitor is a compound of the formula I



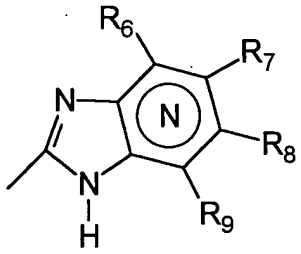
I

wherein

$Het_1$ is



$Het_2$ is



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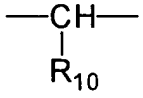

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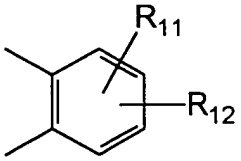

wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by $R_6$-$R_9$ optionally may be exchanged for a nitrogen atom without any substituents;

$R_1$, $R_2$ and $R_3$ are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

$R_6$-$R_9$ are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups $R_6$-$R_9$ form ring structures which may be further substituted;

$R_{10}$ is hydrogen or forms an alkylene chain together with $R_3$; and

$R_{11}$ and $R_{12}$ are the same or different and selected from the group consisting of hydrogen, halogen or alkyl,

with the proviso that the $H^+$, $K^+$-ATPase inhibitor is not pantoprazole.

## CONCLUSION

The Amendment and Remarks set forth herein are fully responsive to the Office Action. It is respectfully submitted that claims 1-11, 18, 19, 26 and 27 are in condition for allowance, which action is earnestly solicited.

Any additional fee in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: 23 July 2001

Respectfully submitted,

John M. Genova
Reg. No. 32,224
Attorney for Applicants

Customer No. 07470
Attorney Direct Dial - (212) 819-8832